

## **REMARKS**

Claims 1-14 are pending and under examination. Applicants have amended claims 1, 6, 12, and 14 to further describe the claimed invention. The specification supports these amendments at, for example, page 3, lines 24-28 and 33-37; page 5, lines 19-27; page 7, lines 20-26; and page 9, lines 31 and 32. Thus, Applicants have not introduced new matter.

The Office rejects claims 1-14 under one or more of 35 U.S.C. §§ 102, 103, and 112. Applicants address these rejections below.

### **Rejection Under 35 U.S.C. § 112**

The Office rejects claims 12 and 13 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Office Action, page 2. According to the Office, the phrases “the colony form” and “the position of a pore” in claim 12 lack antecedent basis. *See id.*

Solely to facilitate prosecution and without acquiescing to the rejection, Applicants have amended claim 12 to recite “a colony form” and “a position of a pore.” Because this amendment renders the Office’s rejection of claims 12 and 13 moot, Applicants request that the Office withdraw this rejection.

### **Rejection Under 35 U.S.C. § 102**

Claims 1, 2, 6, 7, and 11-14 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 02/10349 (“Yamato”). Office Action, page 3. Relying on published US patent application US 2004/0028657 as an English equivalent to Yamato, the Office contends that Yamato teaches a method for producing a multi-layered cultured skin sheet comprising (a) culturing epidermal cells on a cell culture support coated with a

temperature-responsive polymer, (b) bringing the culture temperature below the lower critical solution temperature, (c) bringing the epidermal sheet into close contact with a polymer membrane, (d) peeling the adhering sheet off of the cell culture support together with the polymer membrane, and (e) allowing the cultured cell sheet to adhere to a temperature-responsive polymer, a polymer membrane, or another cellular sheet followed by peeling off the polymer membrane that was in close contact with the epidermal sheet. *See id.* Yamato also allegedly teaches that the multilayered cultured skin sheet is adapted for use in the treatment of burns or wounds. In making this rejection, the Office interprets Yamato's polymer membranes as equivalent to the permeable sheet recited in the rejected claims. *See id.* at page 4. Finally, regarding claims 12 and 13, the Office points to the polymer membranes taught in Yamato for allegedly teaching a means of defining a colony form by controlling a position of a pore because Yamato's polymer membranes allegedly have different pore positions or sizes. *See id.* Applicants traverse.

As the M.P.E.P. instructs, a prior art reference anticipates a claim if that reference teaches "each and every element as set forth in the claim . . . either expressly or inherently" M.P.E.P. § 2131. In the case of independent claims 1 and 6, Yamato does not teach "constructing a three-dimensional tissue with a permeable sheet" or a "A three-dimensional tissue with a permeable sheet." *Arguendo*, even if one were to look at Yamato's polymer membranes as permeable sheets, as the Office does, Yamato's skin cell preparations do not retain the polymer membrane. Specifically, Yamato uses the polymer membrane as a temporary support for the skin cells as a way to improve

the process of peeling off the cell culture from the culture support. See Yamato, paragraphs [0011] and [0013]. Thus, the polymer membrane is only temporarily in contact with the cell culture. After the cell culture is peeled off of the culture support, the polymer membrane is later peeled away as well. See, e.g., paragraph [0019]. The Office acknowledges this in its own description of Yamato's method, stating that the "polymer membrane in close contact is thereafter peeled off to form multiple culture cell layers." Office Action, page 3.

In contrast, the permeable sheet recited in claims 1 and 6 remains in contact with the cultured cells such that a "three-dimensional tissue with a permeable sheet" results. In other words, the permeable sheet is part of the three-dimensional tissue and is not removed during the process of forming this tissue. See, e.g., the specification at page 3, lines 33-37; page 4, lines 34-37; and page 7, lines 20-26. Thus, Yamato cannot anticipate independent claims 1 and 6, and, accordingly, dependent claims 2, 7, 11, and 14.

Regarding claims 12 and 13, as Applicants explained above, the polymer membrane of Yamato only temporarily contacts the cell culture for the purpose of facilitating the removal of the cell culture from the culture substrate and for carrying the removed cells. This limited time of contact between the polymer membrane and the cells is not long enough for the cells to grow on the polymer membrane and be influenced by the pore structure of the polymer membrane, that is, if the polymer membrane was porous. In Yamato, the cell culture grows and forms on the culture support, not on the polymer membrane. See paragraphs [0013] and [0057]. Thus, in

Yamato, the polymer membrane would not influence how colonies of cells form as they grow in culture. For at least this reason, Yamato does not teach the step of “defining a colony form of the cultured cells by controlling a position of a pore in said permeable sheet” as recited in independent claim 12. Yamato therefore fails to anticipate claims 12 and 13. Applicants request that the Office withdraw this rejection of claims 1, 2, 6, 7, and 11-14.

Rejection Under 35 U.S.C. § 103

The Office rejects claims 1-10 under 35 U.S.C. § 103(a) as allegedly obvious over WO 02/088332 (“Mitaka”) in view of U.S. Patent 7,521,231 (“Germain”). Office Action, page 5. Referring to published U.S. application 2004/00073391 as an alleged English equivalent of Mitaka, the Office contends that Mitaka discloses a method of “inducing liver tissue from small hepatocyte colonies by placing the hepatocyte-rich colonies onto a sheet of biocompatible material . . . and further culturing them for a given period of time.” *Id.* The Office also alleges that Mitaka includes collagen sheets, collagen sponges, and polyglycolic acid sheets as biocompatible materials and demonstrates that bile canaliculi form when small hepatocytes were seeded on a collagen sheet or a polyglycolic acid sheet. *See id.*

Acknowledging that Mitaka does not teach constructing a three-dimensional tissue by stacking flat-cultured hepatocytes on a permeable sheet, the Office turns to Germain. According to the Office, Germain teaches a “method for preparing a human or animal tissue by applying a compressive force to a stack of sheets of living tissue thereby inducing adjacent layers to fuse or adhere to each other with each sheet of

living cells is comprised of cells and an endogenous extracellular matrix.” *Id.* at 6. Germain also allegedly suggests that “multi-layer tissue constructs are thicker and therefore stronger and . . . can be designed to more closely resemble the tissues that they intended to replace.” *Id.*

Based on these alleged teachings in Mitaka and Germain, the Office concludes that it would have been obvious to “modify the teachings of Mitaka . . . by forming a multi-layer liver tissue construct by applying compressive force to a stack of sheets made of biocompatible material . . . seeded with cultured small hepatocyte-rich colonies in light of . . . Germain.” *Id.* The skilled artisan would have been motivated to make this combination, the Office reasons, because of the properties of multi-layer tissue constructs allegedly taught by Germain. Applicants disagree.

The teachings of Mitaka and Germain in combination are not compatible. The Office opines that Mitaka discloses a method of “inducing liver tissue from small hepatocyte colonies by placing the hepatocyte-rich colonies onto a sheet of biocompatible material . . . and further culturing them for a given period of time” and cites to paragraphs 24 and 67-72 of the reference. If this were true, then these cell cultures would contain cell colonies cultured on a sheet of biocompatible material. In other words, the sheet of biocompatible material would be present in the cell cultures, given the Office’s interpretation of Mitaka. Such a cell culture construct would not work with Germain’s methods.

Germain instructs that “it is *essential* to be able to fuse adjacent layers of cell tissue together so that the layers are bonded together as firmly and reliably as possible

and resist separation. If these layers of tissue are not fused together well, they may separate or come apart over time. . . .” Col. 1, lines 52-56, emphasis added. Germain does not describe methods that use a substrate akin to Mitaka’s biocompatible material. Rather, Germain describes “a sheet of living tissue” as formed from cells and the extracellular matrix that those cells naturally produce in culture and instructs that “after the sheets of tissue are formed, they are peeled from the dishes.” Col. 8, lines 26-32 and 47-49; col. 11, lines 16-18. Thus, Germain’s sheets of cells do not include exogenous materials such as a biocompatible sheet.

Because, in Germain’s words, it is “essential” to fuse adjacent layers of cell tissue together, one of ordinary skill in the art would not have combined Mitaka’s methods as described by the Office with Germain because the biocompatible sheets that Mitaka’s cells grew on would have prevented the fusion of adjacent layers of cells via Germain’s methods. Given that Germain taught that such fusion was “essential” to the success of making a multi-layered cell culture, the skilled artisan would not have employed Mitaka’s methods to generate each layer to form the multi-layered culture of Germain.

Independent claims 1 and 6, however, recite “a three-dimensional tissue with a permeable sheet.” Given the conflict between the teachings of Mitaka and Germain, the combination of these two would not have rendered claims 1-10 obvious. Applicants therefore request that the Office withdraw this rejection.

Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of claims 1-14.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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